REMARKS

Preliminarily, Applicants respectfully request an interview to review the Declaration evidence submitted herewith relative to the prior art. The undersigned spoke with the Examiner regarding timing of such an interview. The Examiner requested Applicants to file their Preliminary Amendment and Rule 132 Declaration prior to scheduling an interview. Therefore, if the amended claims are not allowable, Applicants respectfully request the Examiner to grant an interview (to include one of the inventors or a representative of the assignee) and to issue a non-final Office Action so as to allow Applicants to submit supplemental test data as may be needed.

Responsive to the objection under 35 U.S.C. § 1.75(c), (as set forth in the Office Action dated July 12, 2001) claims 7, 11, 12, 14 and 15 have been rewritten in independent form. Claim 13 has been canceled.

Responsive to the rejection under 35 U.S.C. § 112, second paragraph, claim 7 has been amended to recite formula (1), where the oxirane derivative of formula (1) satisfies the requirements of claim 1 when subjected to gel permeation and thin layer chromatography. Claim 11 has been similarly amended to recite that the oxirane derivative of formula (1) satisfies the requirements of both claims 1 and 3. Claim 12 is similar to claim 11, but limits R to a CH_3 group. Claim 13 has been canceled, as being cumulative to claim 12. Process claims 14 and 15 have been similarly amended. In claim 14, the oxirane derivative of formula (1) is defined as satisfying the characteristics of claim 1, whereas the oxirane derivative of formula (1) of claim 15 is defined as satisfying the requirements of both claims 1 and 3.

A complete claim set is included above, including claims 1-6 and 8-10 which have not been amended. Claim 13 has been cancelled. Claims 16-43 have been added as new claims.

It is submitted that the amended and other claims presented herein fully comply with 35 U.S.C. § 112, and withdrawal of the foregoing rejection is respectfully requested.

Review and reconsideration on the merits are requested.

Claims 1-6 and 8-10 stand rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent 4,967,016 to Kemp. Claims 1-4, 7, 8 and 11-15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,605,976 to Martinez et al or JP 8-165343 (JP '343). Claims 1-15 were further rejected under 35 U.S.C. § 103(a) as being unpatentable over Martinez et al or JP '343 in combination with Kemp.

The Examiner considered the prior art products to inherently meet the claimed purity requirements. Alternatively, because the prior art is said to teach reducing the water content to achieve a pure alkoxylated compound, the Examiner considered that it would have been obvious to reduce the water content to a level needed to meet the claimed purity requirements.

Applicants traverse, and respectfully request the Examiner to reconsider in view of the Declaration under 37 C.F.R. §1.132 submitted herewith and the following remarks.

The present invention is directed to an oxirane derivative and process for preparation of the same, having a high purity characterized in terms of gel permeation chromatography (GPC) and thin layer chromatography (TLC). The oxirane derivative is useful as a starting material for medical purposes, and particularly drug delivery systems. The oxirane derivative has an adduct

number of 20 to 900, and can be prepared by reacting the compound ROH (where R represents a C_{1-7} hydrocarbon group) with oxirane (ethylene oxide) in a reaction system preferably having a water content of not more than 5 ppm and with a reaction temperature of 50 to 130°C.

For use in drug delivery systems, the oxirane derivative of the present invention must have a high molecular weight (and hence a high adduct number), and must be free from impurities and the products of side reactions. The difficulty in purifying high molecular weight PEG derivatives is illustrated by Y. Oshima et al, "Coating Engineering" Vol. 22, No. 9 (1987) discussed at page 5 of the specification. More particularly, the present inventors discovered that commercial oxirane derivatives, even those sold for pharmaceutical use, have the following impurities.

$RO(C_2H_4O)_nH$ - - - General formula [1]

Wherein R : 1 to 7, n = 20 ~ 900

(A) (GPC) An impurity with an approx. 2-fold molecular weight → due to water present in the reaction system.

(B) (GPC) A compound with a molecular weight lower than that of the desired compound → the compound derived from the by-produced vinyl ether.

(C) (GPC) Deviation of molecular weight distribution from Poisson's distribution → indicating non-uniform reaction.

(D) (TLC) A spot with a different Rf value → indicating an impurity with the same molecular weight as the desired compound but having a different polarity.

The impurities (A) to (D) are described at page 4, line 22 - page 6, line 16 and page 7, line 25 - page 8, line 15 of the specification. The relationship between these impurities and the limitations of claims 1, 2 and 3 is discussed at page 13, line 11 - page 18, line 19 of the specification.

The significance of providing an oxirane derivative (as applied to drug delivery systems) having both a high adduct number and being free of the impurities (A) to (D) is discussed below.

PEG derivatives (such as those defined in claim 7) are used in the pharmaceutical industry to reduce anti-genicity, improve stability, decrease dosage amounts and to protect the drug from being eliminated from the RES system (e.g., the liver and spleen). Generally, a PEG derivative is reacted with a drug molecule which may be an enzyme, or polymer micelle (agglomerate) containing drug molecules, or a liposome encapsulating drug molecules.

With a higher molecular weight PEG, fewer PEG chains are needed to stabilize the drug meaning that more active sites are available after reaction with the PEG derivative. Therefore, the pharmaceutical industry demands PEG derivatives of high adduct number.

As to the impurity (A), this is a diol compound having twice the molecular weight, and the impurity derived therefrom causes problems such as crosslinking of drug molecules. As to impurity (B), this is a compound where the terminal that is by-produced at the ethylene oxide addition reaction is a vinyl group, or a hydrolysate of the compound. If these vinyl ethers are by-produced at the initial or middle stage of the reaction, additional ethylene oxide cannot be added. Thus, these impurities tend to have a lower molecular weight than a target compound. Furthermore, these terminal vinyl ethers are easily hydrolyzed in neutralization and can also be

impurities where the terminal is a hydroxyl group. If such impurity exists, it degrades the binding ratio with drugs and the activity is also lowered. As to impurity (C), this shows a non-uniform MW distribution. A uniform MW distribution is required because an optimum molecular weight varies depending on the structure of enzymes or drugs and the purpose of modification. As to impurity (D), this is an impurity having the same molecular weight as the designed oxirane derivative. This is a vinyl ether compound or a hydrolysate thereof, by-produced at the last reaction stage. It degrades the binding ratio with drugs and the activity is also lowered.

Claim 1 is directed to the compound $RO(C_2H_4O)_n$-H having a certain GPC and TLC purity, whereas claim 7 is directed to a terminal-modified RO(C_2H_4O)n-Xp-Y prepared by aminating or carboxylating the above $RO(C_2H_4O)_n$-H having a certain GPC and TLC purity. It is the compound RO(C_2H_4O)n-Xp-Y having an appropriate functional group that is used to react with a drug, or protein, or micelle, or liposome. If RO(C_2H_4O)n-Xp-Y is prepared from $RO(C_2H_4O)_n$-H having impurities (A) to (D), then the level of impurities is further amplified.

The present invention solves the above-noted problems of the prior art, and provides (i) novel, highly pure oxirane derivatives not heretofore know in the art; (ii) a process for preparation thereof; and (iii) a process for preparation of a terminal-modified oxirane derivative for pharmaceutical use using (i) above as a starting material.

A9

1. **U.S. Patent 4,967,016 to Kemp:**

As the Examiner indicates, Kemp alkoxylates compounds having an active hydrogen and states that the active hydrogen compound can be methylphenol (col. 4, line 33) or C_1-C_{30} alkanol (col. 4, line 42), and that the adduct number can be 30 or greater (col. 8, line 21).

Furthermore, Kemp teaches that the water content of the reactants should be kept low, because water changes the alkylene oxide adduct distribution of the product.

However, the present invention is neither anticipated by nor obvious over Kemp as shown below.

a. Differences in processing result in different end products

Kemp uses barium phosphate as a catalyst which is an essential element of his alkoxylation process (col. 5, lines 47-49, Example 1 at col. 10, lines 30-32, etc.). On the other hand, barium phosphate is not used in the present invention. In the present invention, the water content in the reaction system is more than 5 ppm, and an alkali metal or alcoholate of an alkali metal is used. As demonstrated in the Declaration of Chika Ito submitted herein, this difference in processing provides oxirane derivatives having the purity required by claim 1, which purity cannot be achieved by Kemp.

b. Method of water removal - Kemp

Kemp discloses lowering the water content by heating the mixture of the active hydrogen compound and the catalyst under reduced pressure (not higher than 100 Torr) (column 7, line 55). Also, Kemp states that the water content should not be more than 500 ppm, preferably not more than 200 ppm, to achieve such purpose (column 7, line 49). In practice, (see, Example

10

1 at col. 10, lines 34-36), Kemp heats the reaction system "under a constant nitrogen sparge to drive off water".

However, Kemp's technique for removing water is effective, and even then only marginally so, when the alcohol used as a starting material has a large number of carbon atoms and hence a boiling point considerably higher than that of water. On the contrary, if the alcohol used as a starting material has a small number of carbon atoms (C_{1-7} of the invention) and therefore has a boiling point close to or lower than that of water, water cannot be effectively removed from the reaction system by heating under reduced pressure or by heating in a nitrogen stream (see, page 4, line 1 - page 5, line 4 of the specification).

In Example 1, Kemp applies his technique of distilling under heating in a nitrogen stream or heating under reduced pressure to a raw material NEODOL 23 (Shell Chemical Company) which is a mixture of C_{12} and C_{13} alkanols, where the boiling point of the C_{12} alcohol is 259°C (760 mmHg) and 192°C (100 mmHg) and that of the C_{13} alkanol is higher. Hence, Kemp removes water in Example 1 by heating at 155°C in an autoclave under a nitrogen stream (column 10, lines 30-38). As demonstrated in the Declaration of Chika Ito submitted herewith, this technique is not effective for reducing the water content in practice of the present invention, *where R of the raw material ROH is a C_{1-7} hydrocarbon.* Furthermore, heating under reduced pressure or heating in a nitrogen stream alone cannot reduce the water content of the reaction system to not more than 5 ppm (claim 5) regardless of the carbon number of the starting alcohol. Rather, in the present invention water may be removed from the reaction system by distilling in the presence of metallic sodium, not taught by Kemp

c. Adduct number

Although Kemp suggests that the adduct number can be 30 or greater, Kemp never prepared such products. Furthermore, although Kemp did prepare products including compounds having an number of 20 to 21 (see Example 10 of Kemp), the alkoxylate distribution of the end product was very broad having a molecular weight distribution outside the scope of claim 1. Also, a C_{11}-C_{12} alkanol mixture outside the scope of the present claims was used as a starting material (col. 18, lines 22-24). As demonstrated in the Declaration of Chika Ito submitted herewith, Kemp's method cannot provide a high molecular weight oxirane derivative having the requisite purity.

More particularly, as discussed between pages 6-7 of the specification, if the oxirane derivative has a low molecular weight (i.e., low adduct number), impurities can be removed by distillation. However, when the oxirane derivative has a high molecular weight (i.e., high adduct number), the impurities cannot be removed. This is the case in Kemp. The present invention provides a synthetic method of directly obtaining a high molecular weight oxirane derivative of the requisite purity useful as a starting material of a terminal-modified oxirane derivative for medical purposes. High molecular weight oxirane derivatives free of both high molecular and low molecular impurities, having a polydispersion degree showing good approximation to Poisson distribution and free of impurities having the same molecular weight but a different polarity have not hitherto been obtained.

d. The present claims are not anticipated by Kemp

Even though Kemp generally describes that the active hydrogen compound can be methylphenol or a C_1-C_{30} alkanol and that it is desirable to reduce water content of the reaction system, Kemp never made an oxirane derivative of the invention where R represents a C_{1-7} hydrocarbon group.

For this reason alone, the present claims are not anticipated.

Additionally, although Kemp discloses that the water content is preferably not more than 200 ppm, this is not a specific disclosure of a water content in the reaction system of not more than 5 ppm as required by claims 5 and 9. Thus, for this additional reason claims 5 and 9 are not anticipated by Kemp.

In those instances (i.e., the working examples) where Kemp did prepare an oxirane derivative but using higher alcohols as a starting material, the technique for reducing water employed by Kemp is not effective for reducing water content where a lower alcohol is used as a starting material as required by the present claims. This too is demonstrated in the Declaration of Chika Ito submitted herewith. Thus, Kemp does not disclose an operative method of making an oxirane derivative of formula (1) of the invention where R represents a C_{1-7} hydrocarbon group and having a GPC and TLC purity required by the present claims.

For all of the above reasons, it is respectfully submitted that the present claims are not anticipated by Kemp.

A9

e. Declaration under 37 C.F.R. § 1.132 of Chika Ito

i) Summary of oxirane synthesis and testing

As described in the Declaration submitted herewith, various oxirane derivatives were prepared following the procedure of Kemp and evaluated by GPC and TLC relative to the requirements of present claims 1-3. In Experiment 1 (Compound A), the Kemp catalyst (barium phosphate) was used to synthesize an oxirane derivative from a low-molecular compound (methanol). In Experiment 2, the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) was used to synthesize an oxirane derivative from a higher alcohol C_{12}-C_{13} mixture used as a starting material. Both a lower adduct compound (Compound B of Experiment 2-1) and a higher adduct compound (Compound C of Experiment 2-2) were prepared and tested. In Experiment 3, the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) was used to synthesize an oxirane derivative from benzyl alcohol (a C_7 alcohol) used as a starting material. Both a lower adduct compound (Compound D) and a higher adduct compound were prepared (Compound E).

ii) Summary of test results

The test results shown in Table 1 of the Declaration are reproduced below.

Table 1

	Average number of moles of ethylene oxide added	Gel permeation chromatography			Thin layer chromatography	
		PareaM/ Parea	PareaH/ Parea	A[1])	Rf value	Purity of main spot (%)
Ranges in the claims	20-900 (claim 1)	≥0.85 (claim 1)	≤0.05 (claim 2)	≤0.02 (claim 3)	0.2-0.8 (claim 1)	≥98% (claim 1)
Compound A	1.07*	0.569	0.414	-0.230	Not detectable	not detectable
Compound B	9.05	0.859	0.053	-0.074	0.744	≤88%
Compound C	114.09	0.674	0.304	0.003	0.487	≤81%
Compound D	7.95	0.921	0.037	-0.679	0.679	96.20%
Compound E	13.82*	0.892	0.059	-0.053	0.636	94.70%

A [1]): PMmw/mm - {1 + PtopEOmol/(1 + PtopEOmol)^2}
* Additional ethylene oxide could not be added.

Experiment 1 demonstrates that when the Kemp catalyst (barium phosphate) is used to synthesize an oxirane derivative from a low-molecular compound such as methanol (Compound A), a high-molecular oxirane derivative having the claimed adduct number of from 20 to 900 cannot be obtained. Also, the resulting oxirane derivative does not meet the GPC and TLC requirements of claim 1. Particularly, as shown in Table 1 above, Compound A had an average adduct number well outside the scope of claim 1 even though (in Experiment 1) the maximum

A9

amount of ethylene oxide possible was forced into the reaction system. This is presumably because the barium phosphate catalyst of Kemp has low activity such that the adduct number cannot be substantially increased when a low molecular compound (C_1-C_7) is used as a starting material. Furthermore, Compound A had a GPC purity well outside the scope of claim 1. Also, Compound A could not be separated and could not be detected under the TLC conditions specified in claim 1.

Experiment 2 demonstrates that even when the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) is applied to a higher alcohol C_{12}-C_{13} mixture (which itself is outside the scope of claim 1), the resulting oxirane derivative does not have the required purity. Both a lower adduct compound (Compound B of Experiment 2-1) and a higher adduct compound (Compound C of Experiment 2-2) were prepared and tested. As shown in Table 1 above, Compound B (low adduct number outside the scope of the present claims) was relatively pure in terms of GPC analysis, but did not have a TLC purity of not less than 98% as required by claim 1. In any event, the adduct number of Compound B is outside the scope of claim 1 requiring addition of an average number of moles of oxirane groups of from 20 to 900. In Experiment 2-2, a higher molecular weight compound was prepared having an adduct number of about 114 within the scope of claim 1. However, the resulting Compound C failed to meet the GPC and TLC purity levels required by claim 1.

Experiment 3 demonstrates that when the process of Kemp (barium phosphate catalyst, and heating in a nitrogen stream to remove water) is applied to a C_7 hydrocarbon - benzyl alcohol (Compound D and E), a high-molecular oxirane derivative having the claimed adduct

number of from 20 to 900 cannot be obtained. Also, the resulting oxirane derivative does not meet the TLC requirements of claim 1. Importantly, Kemp's process was unable to provide a product having an adduct number of at least 20 even when the maximum amount of ethylene oxide possible was forced into the reaction system (Compound E).

The above test results show that:

(i) Kemp did not prepare an oxirane derivative having the purity required by claim 1,

(ii) when the Kemp catalyst is used to synthesize an oxirane derivative from a low-molecular compound such as methanol, a high-molecular oxirane derivative having an adduct number of from 20 to 900 required by claim 1 cannot be obtained,

(iii) even when the Kemp process is used to prepare a high-molecular oxirane derivative using a higher alcohol as a starting material (which of itself is outside the scope of claim 1), the resulting compound does not have a GPC and TLC purity as required by claim 1, and

(iv) when the Kemp process is used to prepare an oxirane derivative from a C_7 hydrocarbon, a high-molecular oxirane derivative having an adduct number of from 20 to 900 required by claim 1 cannot be obtained.

This is due to differences in the catalyst and process used for making the oxirane derivative, and the above test data shows that these differences are material to both the purity and adduct number of the end product as defined in present claim 1.

f. The present claims are not obvious over Kemp

As to the underlying obviousness rejection, although Kemp recognized the above impurity (A) resulting from water in the reaction system, Kemp did not recognize problems (B), (C) and (D) associated with preparing oxirane derivatives having a high molecular weight (high adduct number) and prepared from a lower hydrocarbon as a starting material. Kemp made his invention bearing in mind that the polyoxyalkylene derivative thus obtained is to be used for nonionic surfactants, emulsions, solvents and lubricants. In contrast, the present invention was made as a starting material for drugs or pharmaceuticals. Thus, it is understandable that the level of impurity requirements are different between the present invention and Kemp.

The present invention resides not in preparing an oxirane derivative, but in preparing high purity oxirane derivatives suitable for medical use having a high molecular weight and prepared from specific starting materials not amenable to the purification techniques disclosed by Kemp. That is, even if one or ordinary skill could prepare a high molecular weight oxirane derivative using a lower hydrocarbon as a starting material following the technique of Kemp, the resulting oxirane derivative would not have the requisite purity. However, as shown in the Declaration submitted herewith, Kemp's process cannot even provide an oxirane derivative having an adduct number of at least 20 using a C_1-C_7 hydrocarbon as a starting material, let alone one meeting the purity requirements of claim 1. For the above reasons, it is submitted that the present claims are patentable over Kemp.

2. **U.S. Patent 5,605,976 to Martinez et al:**

Claims 1-6 directed to an oxirane derivative represented by formula (1) should be considered separately *relative to Martinez et al* from claims 7-15 directed to an oxirane derivative represented by formula (2) prepared by aminating or carboxylating an oxirane derivative of formula (1). As indicated by the Examiner, Martinez et al uses methoxy PEG as a starting material with a MW level similar to that obtained in this invention (m-PEG-OH : MW - 5,000 : Union Carbide). The methoxy PEG is nominally a compound within the scope of formula (1) of claim 1. As discussed in further detail below, there is no disclosure in Martinez et al relating to the purity of the methoxy PEG starting material or techniques for purifying the methoxy PEG starting material. Rather, Martinez et al used a commercial source of methoxy PEG. Thus, there is no reasonable basis to conclude that the oxirane derivative represented by formula (1) of claim 1 having specific purity requirements with respect to GPC and TLC is unpatentable over Martinez et al.

On the other hand, the purpose of Martinez's invention is to supply high purity polyoxyalkylene derivatives containing carboxyl groups. More specifically, Martinez reacts a polyalkylene oxide (e.g., methoxy PEG) with a tertiary alkyl haloacetate in the presence of a base to form an intermediate tertiary alkyl ester, and thereafter reacts the intermediate with an acid to form a polyalkylene oxide carboxylic acid (col. 2, lines 21-27). The polyalkylene oxide carboxylic acid of Martinez et al is nominally within the scope of the oxirane derivative represented by formula (2) of claim 7.

19

As discussed in the Remarks portion of the Amendment filed April 16, 2001, Martinez et al defines purity of the polyalkylene oxide carboxylic acid by using the conversion rate from the terminal hydroxyl group to carboxyl group as measured by NMR.

The present inventors consider that Martinez et al used commercial m-PEG-OH and did not take into consideration the impurities corresponding to (A), (B), (C) and (D) in the starting material, as distinct from the present invention. There is nothing in Martinez which states that anything other than commercial m-PEG-OH was used. Also, Martinez et al is silent with respect to the purity of the starting m-PEG-OH, and does not consider any techniques for purifying the starting material. As discussed at page 6, lines 17-28 of the specification, if a terminal-modified oxirane compound is synthesized from a commercial oxirane compound containing impurities (such as commercial m-PEG-OH), various impurities are newly produced. Since these impurities have physical properties similar to that of the desired compound, they cannot be effectively removed. This is the case with Martinez.

Furthermore, since the impurity corresponding to (D) has not been know until the present inventors demonstrated the existence thereof, it is natural that Martinez does not take such impurities into consideration.

This difference is demonstrated in the working examples of the present specification. Particularly, the present inventors synthesized derivatives having a terminal carboxyl group using the m-PEG-OH of the present invention and commercial m-PEG-OH (Aldrich) in Example 6 and Comparative Example 5, respectively. Subsequent HPLC analysis demonstrated that the product obtained from the commercial m-PEG-OH contained various impurities. These

results also show that the compounds synthesized by Martinez do not meet the purity requirements of the present claims.

From a different perspective, claims 7-15 are directed to an oxirane derivative (or process for making the oxirane derivative) represented by formula (2), which is prepared by animating or carboxylating an oxirane derivative of formula (1) having GPC and TLC purity levels as defined by claim 1. If the Examiner finds the oxirane derivatives of formula (1) as defined in claim 1 to be patentable, then claims 7-15 which specify use of the high purity oxirane derivative of claim 1 as a starting material must also be patentable. See MPEP §2116.01. Particularly, without knowledge of the new and unobvious oxirane derivative of formula (1) having a GPC and TLC purity as defined in claim 1, one would not find it obvious to use that product to make the oxirane derivative represented by formula (2) of claims 7-15.

3. JP 8-165343:

As stated in the response to the previous Office Action, JP '343 surely shows a GPC chart for the starting material. However, since the x axis of this GPC chart is a logarithmic axis, it is understood that it is recalculated in accordance with the logarithm of molecular weight calculated from the analytical curve. It is impossible to determine the presence or absence of by-products only from the peak that is recalculated.

Also, it is understood from Fig. 3 of JP '343 that the MethoxyPEG-amine synthesized from the starting material includes considerable impurities, and in Example 1 of JP '343, it is subjected to purification by an ion exchange method (ion exchange type liquid chromatography) so as to obtain the MethoxyPEG amine, which has a high purity to some extent. However, since

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the separation is made with an ionic column in the liquid chromatography shown in Fig. 4, the chromatography merely separates ionic substances and nonionic substances. In other words, chromatography does not separate impurities if they have the same ionic properties. Namely, when the hydroxyl group at the terminal end for impurities different in molecular weight distribution, and for impurities that are the same in molecular weight but different in molecular weight distribution, are converted to amine as in MethoxyPEG-OH, the converted impurities cannot be analyzed with liquid chromatography. This is because they have substantially the same ionic property.

In Examples 8 and 9 and Comparative Example 7 of the present specification, MethoxyPEG amines were synthesized using the MethoxyPEG-OH of the invention and commercial MethoxyPEG-OH. Each of them showed substantially similar purities in terms of amine value-converted purity. However, when induced into a block polymer as an application example thereof, they were found to have greatly different physical properties.

Applicants submit herewith an English translation of JP '343 for review and consideration by the Examiner. As described in paragraph [0015], JP '343 relates to a process for producing a high purity polyoxyalkylenemonoamine easily without using special raw materials, reacting equipment and catalyst. JP '343 is similar to Martinez, and does not consider at all the impurities in methoxy polyethylene glycol as a starting material. Figs. 1 and 2 only confirm that the by-product polyamine is not generated in the cyanoethylation step. However, JP '343 is silent with respect to the by-product diol and impurities found with TLC. That is, JP

'343 does not describe the production method of the invention needed to obtain the claimed high purity oxirane derivatives.

4. Combination of Martinez et al or JP '343 with Kemp:

Regarding the Examiner's position that it would have been obvious to modify Martinez et al or JP '343 to achieve the oxirane derivatives having the requisite purity based on Kemp (teaching that it is important to keep water content low during the reaction to achieve a high purity product), the test data presented in the Declaration under 37 C.F.R. § 1.132 submitted herewith shows that Kemp's process cannot provide an oxirane derivative having both an adduct number and meeting the GPC and TLC requirements of claim 1. In fact, the Kemp process cannot even provide an oxirane derivative having an adduct number of at least 20 using a C_1-C_7 hydrocarbon as a starting material, let alone one meeting the purity requirements of claim 1. Therefore, even if one of ordinary skill were to apply Kemp's technique to Martinez et al or JP '343, the inventive oxirane derivative still cannot be obtained.

For the above reasons, it is respectfully submitted that the present claims are patentable over Martinez et al and JP '343, alone or in combination with Kemp.

5. Gist of the Invention:

As described in the specification, the present invention provides a high molecular weight oxirane derivative having a narrow molecular weight distribution, a low impurity content and a high purity useful as a starting material of terminal modified oxirane derivatives for pharmaceutical purposes, particularly for chemical modification of physiologically active

40

proteins such as polypeptides and enzymes and chemical modification in drug delivery systems like liposome, polymer micelle, etc., and a process for the preparation thereof.

The present invention relates to an oxirane derivative having few impurities of (A), (B), (C) and (D), especially few impurities of (A) and (D) as recited in claim 1. As explained above, oxirane derivatives satisfying the above conditions were not attained, and are not obvious from the references cited by the Examiner.

It may be sure that some of the cited references describe the same or similar chemical substances structurally. However, the kinds of impurities permitted or the permitted amounts thereof depend on the particular requirements of different technical fields. Even if the cited references are referred to, the high purity oxirane derivative of the present invention cannot be obtained as shown above. More particularly, none of the cited references teach a method of providing an oxirane derivative having an adduct number of at least 20 where a compound ROH which is C_{1-7} hydrocarbon is reacted with oxirane and the water content is not more than 5 ppm. This difference in processing provides a high purity oxirane derivative of the invention distinct from those of the cited references.

Withdrawal of all rejections and allowance of claims 1-12 and 14-43 is earnestly solicited.

In the event that the Examiner believes that it may be helpful to advance the prosecution of this application, the Examiner is invited to contact the undersigned at the local Washington, D.C. telephone number indicated below.

Respectfully submitted,

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